REMARKS

Restriction Requirement and Amendment of the Claims

The Applicants thank the Examiner for rejoining Groups I-III. In order to expedite prosecution, the claims have been amended to remove nonelected subject matter.

Additionally, in Claim 1, the Applicants have amended the optional substituents on the piperidinyl ring of -A-R^7 and also have amended the R^6 and R^7 groups to more particularly point out and distinctly claim their invention. Claim 8 has been amended to depend from claim 1. Claim 13 has been amended to more particularly point out and distinctly claim their invention.

Specification Objection

The Applicants have amended the title and respectfully request that the Office withdraw the objection that the title is not descriptive.

Claim Rejections – 35 USC § 112, 1st Paragraph

Claims 1-9, 12-19, and 31-38 are rejected as not enabled for other than compounds where R^{13} is "H, alkoxy, amino, alkylamino, and heteroalicyclic where heteroalicyclic compounds are morpholino, pyrrolidinyl, and piperidinyl; R^4 and R^5 fused to form phenyl; and R^{10} being H, alkyl, alkoxy, cyano, halo, [and] haloalkyl" (page 3-4, Office Action). The Office Action goes on to state that the Application does not reasonably provide enablement for "R^{13} being all claimed heteroalicyclic compounds, R^4 and R^5 being all fused rings claimed and R^{10} being all substituents claimed" (page 4). Applicants respectfully request reconsideration of this rejection for the following reasons.

The Applicants respectfully point out that the restriction group they elected does not allow R^4 and R^5 to be "all fused rings claimed." The elected group limits R^4 and R^5 to individual groups or limits R^4 and R^5, when taken together, to a fused phenyl only. The claims were amended to remove nonelected subject matter; and as a result, R^4 and R^5 do not form fused rings other than phenyl. The Office regarded the R^4/R^5 phenyl as enabled on page 3-4 of the Office Action. For this reason, the Applicants believe that the enablement rejection with respect to R^4 and R^5 is moot and respectfully request reconsideration.

In order to make a non-enablement rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided. (M.P.E.P. § 2164.04). To make a prima facie case of non-enablement, he or she must prove that the applicants have not shown how to make and use the invention without undue experimentation in a manner commensurate with the scope of the claims (MPEP § 2164.01). The examiner must make specific findings of fact, supported by evidence, which would allow a conclusion of non-enablement (M.P.E.P. § 2164.04). Conclusory statements, unsupported by a factual basis, are not sufficient to meet this burden.

In this case, the Office has not met its initial burden. The Patent Office has not made findings, specific to this case, identifying "why one skilled in the art could not supply the information without undue experimentation" (M.P.E.P. § 2164.04). Here, the Office reaches the conclusion that the Specification provides limited guidance for the entire scope but does not consider or discuss what a person of ordinary skill in the art would know with respect to the compounds in Applicants' scope and does not offer any *specific* evidence for why the information the Office perceives as missing could not be supplied. Accordingly, the Applicants respectfully submit that the Office has not made a prima facie case of non-enablement.

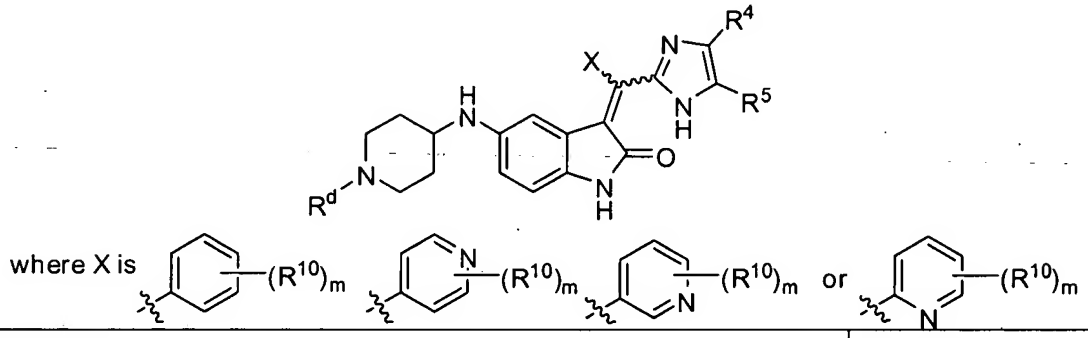
In particular, with respect to the "heteroalicyclic" of R^{13}, the Office stated that R^{13} is enabled for morpholino, pyrrolidinyl, and piperidinyl but not the term heteroalicyclic. The Office has offered no specific finding of why a person of ordinary skill in the art would not know how to make and use the full scope of the heteroalicyclic term in R^{13} without undue experimentation. Applicants respectfully point out that there is no requirement that all the compounds claimed by the genus be prepared and tested for the specification to be enabling. (See *In re Angstad,* 190 USPQ 214, 218 (CCPA 1976).) The Applicants have provided representative examples of the heteroalicyclic ring and submit that the full scope of the R^{13} heteroalicyclic is thus enabled.

Even if the Office had made a prima facie case of non-enablement, the Applicants have clearly shown how to make and use the invention enabling one of skill in the art to practice the invention without undue experimentation. The Office states that R^{10} is only enabled for H, alkyl, alkoxy, cyano, halo, and haloalkyl and that R^{13} is only enabled for H,

alkoxy, amino, alkylamino, morpholino, pyrrolidinyl, and piperidinyl. The Applicants respectfully direct the office's attention to specific examples in the Specification which provide support for the full scope of the current claims. See Table 1 for a listing of groups which the Office has not identified as enabled but for which the Applicants provided an example in the Specification.

Table 1

R^d represents the optional substituent on the R^7 piperidinyl in claim 1, the R^{12} group in claim 9, and the $-R^{12}-R^{13}$ group in claims 12 and 13.



	Group	Example
R^{10}	$-NO_2$	Table 1, entries 7, 19
R^{10}	$-NH_2$	Table 1, entries 11, 21
R^{10}	$-C(=NR^8)NR^6R^7$	Table 1, entry 23
R^d	Claim 1: where the optional substituent on the piperidinyl ring is arylalkyl Claim 9: where the R^{12} substituent on the piperidinyl ring is C_{1-8}alkyl optionally substituted with aryl	Table 1, entries 1, 34
R^d	Claim 1: where the substituent on the piperidinyl is optional (H) Claim 9: where the R^{12} substituent on the piperidinyl ring is H	Table 1, entries 22, 81
R^d	Claim 1: where the substituent on the piperidinyl is sulfonyl Claim 9: where the R^{12} substituent on the piperidinyl ring is $-SO_2R^6$ and R^6 is alkyl	Table 1, entries 30, 93
R^d	Claim 9: where the R^{12} substituent on the piperidinyl ring is C_{1-8}alkyl substituted with dialkylamino Claims 12, 13: where R^{12} is alkylene and R^{13} is dialkylamino	Table 1, entries 29, 84

Thus, the specific examples provide enablement for more than where R^{13} is "H, alkoxy, amino, alkylamino, and heteroalicyclic where heteroalicyclic compounds are morpholino, pyrrolidinyl, and piperidinyl; ... and R^{10} being H, alkyl, alkoxy, cyano, halo, [and] haloalkyl" and request reconsideration of this rejection.

In addition to disclosing specific working examples for representative R^{10} and R^{13}

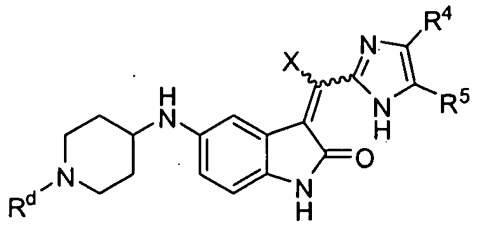
groups, the Application describes how to make compounds of the invention in the section entitled "Synthesis of Compounds" of the Specification (pages 65-78 of the Specification). One of ordinary skill in the art can make the compounds whose synthesis is not specifically described in this Application, by using what is disclosed in conjunction with what is known in the art. With respect to R^{10}, using the disclosure in Example 1 on page 65 of the Specification and the methods known to one of skill in the art, the full scope of R^{10} can be introduced using acid chlorides which are known in the art or can be prepared using procedures analogous to those given below. See Table 2 for a listing of literature methods useful for preparing acid chlorides which can be used in the synthesis of a Compound of the Invention.

Table 2

Preparation of Intermediates Useful in the Synthesis of a Compound of the Invention

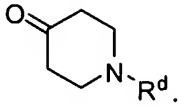
Claimed R^{10} Group	Reference Describing Examples of the Above Reaction
R^{10} is $-OR^6$ where R^6 is H	*J. of Chemical and Engineering Data* **1982,** *27(4),* 479-81
R^{10} is $-OR^6$ where R^6 is arylC_{1-8}alkyl	*Zeitschrift fuer Chemie* **1985,** *25(9),* 329-30
R^{10} is $-C(O)R^7$ where R^7 is alkyl	*J. of Medicinal Chemistry* **1999,** *42(1),* 153-163
R^{10} is $-CO_2R^6$ where R^6 is H	*Gazzetta Chimica Italiana* **1987,** *117(9),* 529-31
R^{10} is $-SR^6$ where R^6 is aryl	*J. of Medicinal Chemistry* **1976,** *19(6),* 798-802
R^{10} is $-NR^6R^7$ where R^6 is H and R^7 is alkyl	*Zhurnal Obshchei Khimii* **1946,** *16,* 1033-40
R^{10} is $-N(R^6)SO_2R^6$ where the 1st R^6 is H and the 2nd is alkyl	*European J. of Medicinal Chemistry* **1977,** *12(1),* 81-6
R^{10} is $-C(O)NR^6R^7$ where R^6 is H and R^7 is aryl	*Bulletin de la Societe de Pharmacie de Lille* **1977,** *33(1),* 67-77
R^{10} is $-S(O)_2R^6$ where R^6 is aryl	*J. of Polymer Science* **1959,** *40,* 359-66
R^{10} is $-SO_2NR^6R^7$ where R^6 and R^7 are alkyl	*Tetrahedron Letters* **1983,** *24(30),* 3137-40
R^{10} is R^7 is aryl	U.S. 4,473,709 (25 Sep 1984)
R^{10} is R^7 is heterocyclyl	*Bull. of the Chem. Soc. of Japan* **1985,** *58(8),* 2192-6

With respect to the substituents on the piperidinyl ring (as represented by R^d below),



(where R^d represents the optional substituent on the R^7 piperidinyl in claim 1, R^d represents R^{12} in claim 9, and R^d represents R^{12}-R^{13} in claims 12 and 13), a person of ordinary skill in the art would know how to make the full scope of R^d by using the same or analogous conditions as disclosed in Example 6 on page 68-9 of the Specification.

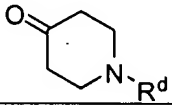
The ketone starting material of general formula



is commercially available and/or well known in the literature. For just a few examples see Table 3.

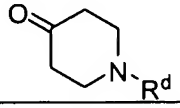
Table 3.

R^d represents the optional substituent on the R^7 piperidinyl in claim 1, R^{12} in claim 9, and -R^{12}-R^{13} in claims 12 and 13.



	Claimed Group	**Literature Reference**
R^d	Claim 1: where the substituent on the piperidinyl is acyl Claim 9: where the R^{12} substituent on the piperidinyl ring is -C(O)R^7 and R^7 is $C_{1\text{-}8}$alkyl or aryl	commercially available
R^d	Claim 1: where the substituent on the piperidinyl is sulfonyl	commercially available
R^d	Claim 1: where the substituent on the piperidinyl is aryl	*J. of the Amer. Chem. Soc.* **1930,** *52,* 1030-2
R^d	Claim 1: where the substituent on the piperidinyl is heterocyclyl	*Organic Letters* **1999**, *1(8),*1261-1262
R^d	Claim 1: where the substituent on the piperidinyl is heterocyclylalkyl Claim 9: where the R^{12} substituent on the piperidinyl ring is $C_{1\text{-}8}$alkyl optionally substituted	*Heterocycles* **1998**, *48(2),* 239-242

R^d represents the optional substituent on the R^7 piperidinyl in claim 1, R^{12} in claim 9, and $-R^{12}-R^{13}$ in claims 12 and 13.



	Claimed Group	Literature Reference
	with heterocyclyl	
R^d	Claim 9: where the R^{12} substituent on the piperidinyl ring is $-CO_2R^6$ where R^6 is C_{1-8}alkyl or arylC_{1-8}alkyl	commercially available
R^d	Claim 9: where the R^{12} substituent on the piperidinyl ring is $-C(O)NR^6R^7$	*J. of Organic Chemistry* **1990,** *55(8),* 2552-4
	Claim 9: where the R^{12} substituent on the piperidinyl ring is C_{1-8}alkyl substituted with aryloxy or C_{1-8}alkyl substituted with alkoxy	*Helvetica Chimica Acta* **1966,** *49(7),* 2370-94
R^d	Claim 12, 13: where R^{12} is alkylene and R^{13} is heteroalicyclic in the $-R^{12}-R^{13}$ substituent on the piperidinyl ring	GB919124 (published in 1963)

The Applicants submit that they have shown how to make the full scope of their claimed invention when the disclosure is considered in light of what a person of ordinary skill in the art knows.

In addition to showing how to make the full scope of the claims, the Applicants have shown how to use the full scope of the claimed invention by providing assays by which a compound can be tested to determine its activity (pages 78-81 of the Specification). The Applicants obligation is only to *show how* to use and they have done this by providing the methods to test the compounds; however, they have gone further by including biological information for 118 compounds. (See Table 3 on pages 81-93 of the Specification). The working examples provided in the present specification provide one of ordinary skill in the art ample enabling support for how to use the entire genus of compounds claimed.

In summary, the Applicants respectfully submit that Patent Office has not met its burden to show a prima facie case of non-enablement of the full scope of R^{10} and R^{13} as it has not provided specific findings of why a person of ordinary skill in the art could not practice the invention without undue experimentation. Even if the Office had met its burden, a person of ordinary skill in the art, given the disclosure in the Specification and

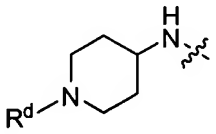
what is well-known in the art, would know how to make and use the entirety of Applicants' claimed scope. The Applicants therefore, respectfully request reconsideration and withdrawal of this rejection.

Claim Rejections – 35 USC § 103

The Applicants thank the Examiner for clarifying that there is a typographical error on page 10 of the Office Action. For the record, Applicants note that the reference in the sentence on page 10 which begins "US '806 differs from the instant application at ..." should be US '429 instead.

The Office has rejected Claims 1-9, 12-19 and 31-38 as being unpatentable over Tang US 6,689,806 (US '806) in view of Tang US 6,316,429 (US '429) and in further view of Tang US 6,569,868 (US '868). The Applicants respectfully submit that the references, either alone or in combination, do not teach or suggest their invention to one skilled in the art and further do not provide a reason or motivation to make the specific molecular modifications necessary to achieve Applicants' invention.

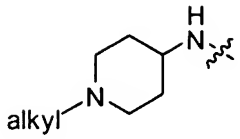
The Applicants respectfully submit that the Office has misconstrued the differences between the prior art and Applicants' invention when doing the Graham analysis. The Applicants submit that none of US '806, US '429, and US '868 teach or suggest Applicants' substitution on the indolinone, as depicted below,



where R^d represents the optional substituent on the R^7 piperidinyl in claim 1, R^d represents R^{12} in claim 9, and R^d represents R^{12}-R^{13} in claims 12 and 13.

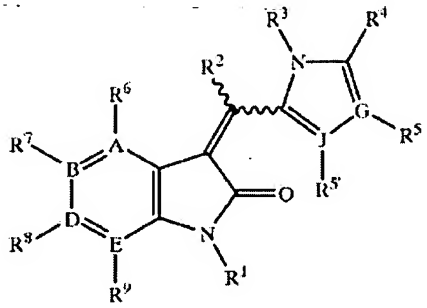
With regard to US '429, the indolinone in the reference can be substituted with -$NR^{10}R^{11}$, but neither R^{10} nor R^{11} independently can be a heteroalicyclic group. The Applicants respectfully wish to draw the Office's attention to the definition of R^{10} and R^{11}. R^{10} and R^{11} are defined as "independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen" (column 5, lines 38-49; emphasis added). R^{10} and R^{11} must be taken together or "combined" to form a

heteroalicyclic. US '429 does not, in fact, teach



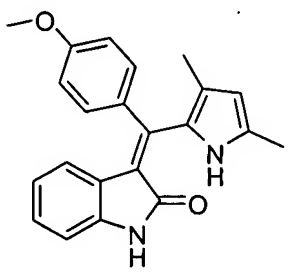
as stated by the Office (page 10 of the Office Action).

With regard to US 6,569,868, the Office did not point out specifically where the reference "discloses species and teachings as claimed in the instant application" (page 14). Nevertheless, the Applicants note that US '868 also does not disclose Applicants'-NH-heteroalicyclic substitution on the indolinone ring. In the structure in column 4 of US '868,



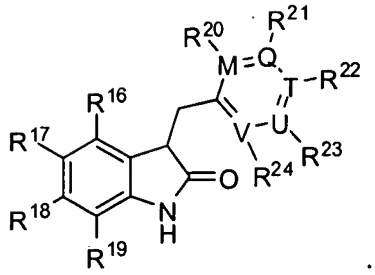
R^7 can be $-NR^{10}R^{11}$ but neither R^{10} nor R^{11} independently can be a heteroalicyclic group. R^{10} and R^{11} only form a heteroalicyclic <u>when combined</u> with the nitrogen to which they are attached (column 5, lines 14-15). The US '868 does not, in fact, teach Applicants' -NH-heteroalicyclic group.

US '806 also does not teach the -NH-heteroalicyclic substitution. The compound cited by the Office



US '806 Compound (column 79)

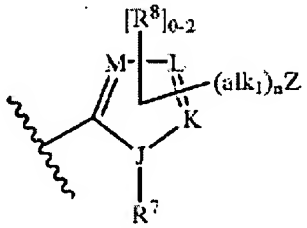
(page 9, Office Action) is unsubstituted, i.e. not substituted with Applicants' –NH-heteroalicyclic. With regard to column 13 of US '806,

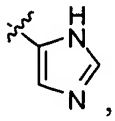


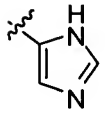
the indolinone can be $NR^{25}R^{26}$ and R^{25} can be hydrogen and R^{26} can be heteroaryl (as noted by the Office on pages 13-14 of the Office Action). Neither R^{25} nor R^{26} can be heteroalicyclic, and therefore Applicants' -NH-heteroalicyclic substitution is not taught.

In summary, none of the cited references teach Applicants' -NH-heteroalicyclic group. In light of how the Office read the references, the Applicants submit that the Office's basis for making a rejection for obviousness is not supported and respectfully request consideration of this rejection. Notwithstanding, the Applicants' invention is not obvious for the following reasons.

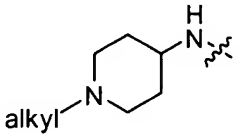
The Applicants submit that US '429 does not, in fact, teach a positional isomer of Applicants' invention and therefore does not support a prima facie case of obviousness. The Office states that the only difference between the reference and Applicants' invention is that the imidazolyl of the reference is "bonded to the 4-position [sic] as compared to the 2-position" (page 10). The Applicants respectfully disagree. US '429 does not teach an unsubstituted imidazol-5-yl. The group Q in US '429 at column 5, depicted below,



must be substituted with "$(alk_1)_nZ$" where n is 1 to 10 and Z is a "polar group." The Applicants thus assert that US '429 does not in fact teach  , but actually teaches

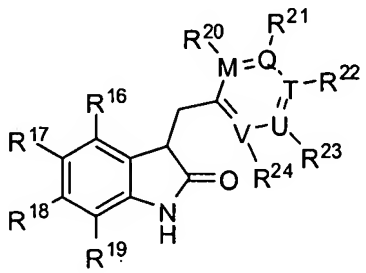


substituted with "$(alk_1)_nZ$" group. In the instant claims, R^4 and R^5 (the substituents on their 5-membered heteroaryl) do not include a substituted alkyl. In addition, as discussed above, US '429 does not teach



as stated by the Office. Considering the differences between the disclosure in US '429 and Applicants' invention, the Applicants submit that US '429 does not disclose a positional isomer. Further, the disclosure in US '429 is not so structurally similar as to provide a teaching, suggestion, or motivation for making the specific chemical modifications necessary to arrive at Applicants' invention. US '429 does not support a legal conclusion that the instant claims would have been *prima facie* obvious.

The Office states that the disclosure of US '429 when combined with the disclosure in US '806 renders Applicants' invention obvious. The Applicants respectfully disagree. In chemical cases, the prior art must "have suggested making the specific molecular modifications necessary to achieve the claimed invention" (*Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd,* 83 USPQ2d 1169, (Fed. Cir. 2007) at1174). As discussed above, neither US '806 nor US '429 teach or suggest Applicants' –NH-heteroalicyclic substitution. The US '806 Compound cited by the Office (see above) is unsubstituted. The indolinone in US '429 can be substituted with $NR^{10}R^{11}$, but R^{10} and R^{11} cannot independently be a heteroalicyclic group. In the disclosure of US '806 at column 13,



the indolinone can be $NR^{25}R^{26}$ and R^{25} can be hydrogen and R^{26} can be heteroaryl. In Applicants' invention, the substitution on the indolinone is an –NH-heteroalicyclic group, i.e. is not aromatic. Saturated rings are structurally different from aromatic rings and are not expected to have similar properties. There is no suggestion or teaching that would have motivated a person of ordinary skill in the art to 1) pick the imidazol-5-yl in US '429 from a list of twenty 5-membered heteroaryl groups and remove the Z group from the required $-(alk_1)_nZ$ substitution, 2) replace the pyrrolyl in the US '806 Compound with the 5-membered heteroaryl group crafted in 1), 3) take the -NH-heteroaryl from column 13 of US '806 and change the heteroaryl to a heteroalicyclic, and 4) substitute the core generated by 1) and 2) with the group crafted in 3) to arrive at Applicants' invention. The Office offers no reason or motivation to combine US '806 and US '429 to make all of the chemical modifications necessary to arrive at Applicants' invention.

In summary, since none of the references teach or suggest the -NH-heteroalicyclic substitution on the indolinone, no combination of references will arrive at Applicants' invention. There is no motivation or suggestion in the art to make all the changes to the disclosure in the references that would be necessary to achieve Applicants' claimed invention. A legal conclusion that the instant claims would have been *prima facie* obvious is not supported and the Applicants respectfully request reconsideration of this rejection.

SUMMARY

In view of the foregoing, the Applicants believe the Application is in condition for allowance and respectfully request entry of the amendments and reconsideration of the objections and rejections for the above given reasons. It is not believed that a fee is due with the submission of this response. Should any fees be required by the USPTO in

order to process this submission and the papers attached, the Commissioner is hereby authorized to charge the necessary fees to Deposit Account Number 50-1108.

Respectfully submitted,

October 23, 2008
Date

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